Journal of Surgical Oncology 1999;71:140–146

Doubling Time of Serum CA 19-9 in the Clinical Course of Patients With Pancreatic Cancer and its Significant Association With Prognosis

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Background and Objectives: Pancreatic cancer is generally a disease with a poor prognosis, and relationship between change of serum CA 19-9 level and progression of this disease was investigated with regard to clinical pace of disease and tumor growth.

Methods: CA 19-9 doubling time was examined in 75 patients with pancreatic cancer, including 41 inoperable cases. Then, its relation with their prognosis and change in tumor was evaluated.

Results: The doubling time of CA 19-9 and CEA could be calculated in 90.2% and 58.5% of patients with inoperable pancreatic cancer. CA 19-9 doubling time was clearly associated with survival time in inoperable and palliatively operated cases, but not with sex, age, site of the lesion, or liver metastasis, and was significantly correlated with the tumor volume doubling time.

Conclusions: Examination of CA 19-9 doubling time may be useful in clinical evaluation of the prognosis for patients with pancreatic cancer and could possibly prove valuable in terms of the analysis of the growth process in this disease. *J. Surg. Oncol. 1999;71:140–146.*

KEY WORDS: **growth of pancreatic cancer; tumor marker doubling time; CA 19-9; CEA (carcinoembryonic antigen); prognosis**

INTRODUCTION

Some of the tumor-producing substances such as CA 19-9 [1] or carcinoembryonic antigen (CEA) [2] are now used clinically as tumor markers for the diagnosis and follow-up of patients with cancer. For example, it is reported that CA 19-9 reduction may be useful for assessing the efficacy of chemotherapy for advanced pancreatic cancer [3]. However, proper quantitative evaluation of the increase in time in measured serum levels of such tumor marker or its detailed relationship with their prognosis has yet to be studied in depth.

At present, accurate determination of tumor size in pancreatic cancer, or definite analytic estimation of the growth rate of pancreatic cancer from the results of general imaging techniques are not always easy [4]. Time-course analysis of changes in the serum tumor marker levels in monitoring patients with cancer of the pancreas is considered to be important to further clarify the clinical usefulness in measurement of circulating tumor markers.

Therefore, in this study, we calculated "tumor marker doubling time," i.e., the time needed for a serum tumor

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Accepted 10 April 1999

marker level to be doubled, in each of the patients. We also evaluated its relationship with the prognostic survival time of those patients with change in cancerous tumor growth in the clinical course of pancreatic cancer.

MATERIALS AND METHODS

The subjects were 75 pancreatic cancer patients (38 males and 37 females) ranging in age from 39 to 93 years, who did not receive any anticancer treatment such as chemotherapy or radiotherapy. Informed consent was obtained, and procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Of these patients, 41 were inoperable, 21 underwent palliative surgery such as cholangioenterostomy, 9 had recurrence after resectable operation, and 4 were without any recurrence after radical resection of the tumor. Diagnosis of pancreatic cancer was made by autopsy, operation, or data obtained by ultrasonography, computed tomography (CT), and angiography. Pancreatic cancer was classified according to the general rules for the study of pancreatic cancer of the Japan Pancreas Society [5].

The serum level of CA 19-9 and CEA was determined with a CA 19-9 RIA kit (Centocor, PA) and the CEA RIA kit (Dainabot, Tokyo, Japan). CA 19-9 level exceeding 37 U/ml or CEA level over 2.5 ng/ml were regarded as abnormal, as indicated in the instructions of the kits. Those tumor marker levels were measured, in principle, more than three different times in each patient. A semilogarithmic graph was prepared in each subject with the observation time revealed as number of days plotted along the X-axis and the tumor marker level (logarithm) along the Y-axis. A regression analysis was then performed by a computerized calculation when the tumor marker level showed a stable increase and the doubling time (DT) was obtained from the formula of $DT = (\log 2)/a$ using the slope of the calculated regression line ($Y = aX + b$) (Fig. 1). When no significant increase in the tumor marker level was observed during the follow-up period, calculation of DT was considered to be impossible.

In 12 of the subjects, the image of the pancreatic or metastatic tumor was followed by CT or ultrasonic examination and each volume was estimated from the long and short diameters in the largest section of the tumor. Then, "tumor volume doubling time" as a measure of growth was calculated [6] and compared with the tumor marker doubling time. Immunohistological examination of tumor markers was carried out as reported previously [7,8].

Statistical analysis was made with the Wilcoxon rank-sum test or Kruskal-Wallis test. *P* values were derived from two-tailed tests, and differences were considered significant if $P < 0.05$.

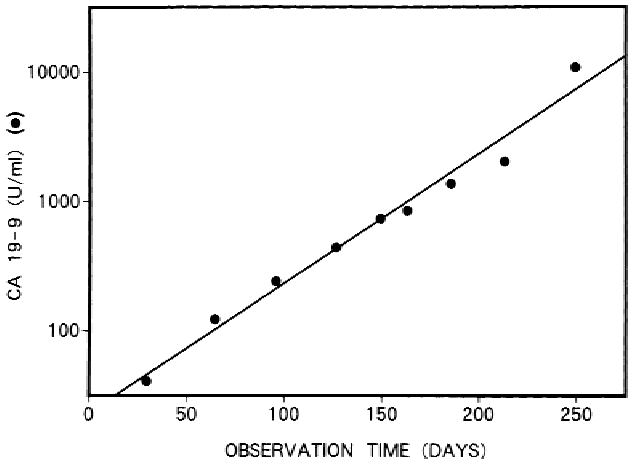

Fig. 1. Relationship between the observation time (X) and the increase of serum CA 19-9 level (logarithm: Y) in the example case of inoperable pancreatic cancer (case number 35 in Table I). The CA 19-9 doubling time was calculated to be 30.4 days from the slope of the linear regression line ($Y = aX + b$, $a = 0.009889$, $b = 1.398$, $r = 0.989$, $P < 0.0001$) approximating the correlation curve of time and CA 19-9 concentration.

RESULTS

Case Presentation

This 55-year-old male was admitted for close evaluation of disturbed glucose metabolism, and an abnormal CA 19-9 level of 289 U/ml was found. Subsequent examinations including CT and endoscopic retrograde pancreatography suggested cancerous tumor at the tail of the pancreas. Surgical operation was performed on the 92nd day after the start of observation. After resection of the tumor by caudal pancreatectomy, the patient showed an uneventful course for a while, and the serum level of CA 19-9 was once normalized to 29 U/ml, but, it began to progressively increase from the 65th day after operation (Fig. 2). The serum level of CEA also began increasing from the 189th day after operation.

No clear signs of liver metastasis were noted preoperatively, but abdominal CT taken on the 307th day after operation showed a space-occupying lesion of liver metastasis, and the progressive increase in the size of the metastatic lesion was observed on CT images taken on the 368th, 454th, 503rd, and 532nd day after operation.

In this case, CA 19-9 and CEA continued to increase upon relapse until the death of the patient on the 532nd day after operation. This increase in the serum CA 19-9 level was significantly correlated with the duration time ($r = 0.988$, $P < 0.001$) during the period of its continuous increase, and CA 19-9 doubling time was calculated to be 42.3 days in this period. The serum CEA level also showed a significant correlation with the time ($r = 0.993$, $P < 0.001$) in observation , and its doubling time was calculated to be 35.7 days. The liver tumor observed by abdominal CT was proven to be a metastatic lesion of

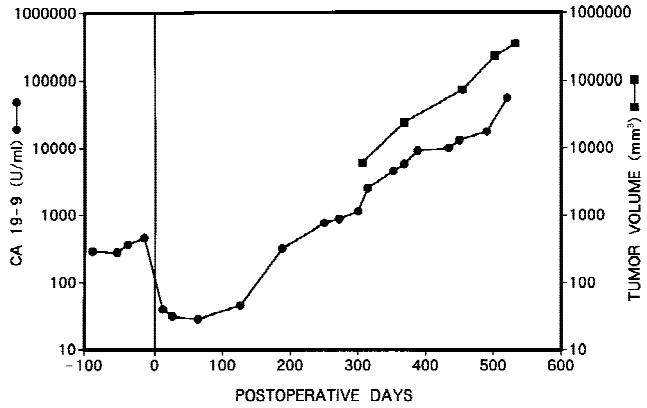

Fig. 2. Changes of serum CA 19-9 level and tumor volume in the clinical course of an operated patient with pancreatic cancer (case number 68 in Table II) showing a recurrence and metastasis to the liver after the resection. The serum CA 19-9 decreased after the operation, but then exhibited a continuous increase, and the tumor volume of liver metastasis also showed a continuous increase indicating a significant correlation with the serum CA 19-9.

pancreatic cancer, and the increase in the tumor volume estimated from CT images obtained at five different postoperative times correlated significantly with the time ($r = 0.995$, $P < 0.001$) during this observation period. The doubling time of the tumor volume was calculated to be 39.3 days, which was comparable to the doubling time of the tumor markers.

Recurrent adenocarcinoma in the remnant pancreatic tissue, and its metastasis to the liver, lungs, kidneys, and the heart, was confirmed by pathological examination at autopsy. Immunohistological examinations by an enzyme antibody technique showed marked positivity of both CA 19-9 and CEA in cancer cells of the primary pancreatic cancer tissue, and metastatic tumor tissues of the liver and other organs.

CA 19-9 Doubling Time in Pancreatic Cancer Patients

Data of patients with pancreatic cancer in this study is summarized in Table I for inoperable cases and Table II for operated cases including Case No. 68 presented above. The CA 19-9 doubling time, which was calculable in 90.2% (37/41) of the inoperable cases, was 6.1–313.0 days (mean 47.1 days, median 36.5 days). It was also calculable in 81.0% (17/21) of palliatively operated cases and was 3.2–153.5 days (mean 53.6 days, median 37.2 days). It was calculable in all recurrent cases (9/9) during recurrence and was 13.8–94.7 days (mean 43.4 days, median 42.1 days). However, no significant elevation in serum CA 19-9 level was observed in four cases without recurrence after radical resection of the tumor. No significant difference was observed in the CA 19-9 doubling time among the inoperable, palliatively operated, and recurrent groups ($P = 0.8504$).

CEA Doubling Time in Pancreatic Cancer Patients

The CEA doubling time, calculated in 58.5% (24/41) of inoperable cases, was 3.6–168.1 days (mean 63.9 days, median 52.8 days). It was calculated in 61.9% (13/21) of palliatively operated cases and was 12.3–152.3 days (mean 71.8 days, median 60.8 days). It was calculated in 55.6% (5/9) of the recurrent cases and was 29.8–117.3 days (mean 54.7 days, median 47.4 days), but there was no increase of serum CEA in the operated cases without recurrence. No significant difference was observed in the CEA doubling time among the inoperative, palliatively operated, and recurrent groups ($P = 0.8663$).

Relationship Between CA 19-9 Doubling Time and Survival Time

The patients in this study all died during the follow-up except four cases that did not have a relapse after resectable operation. A significant correlation ($r = 0.744$, $P < 0.0001$) was observed in the group of inoperable cases between CA 19-9 doubling time and survival time (number of days for observation from its start to the death of the patient). In the palliatively operated cases, also, the CA 19-9 doubling time was correlated significantly with time of whole survival period ($r = 0.635$, $P = 0.0062$) and postoperative period from operation to the death ($r = 0.625$, $P = 0.0073$).

Although no correlation was observed between CA 19-9 doubling time and survival time ($r = 0.590$, $P = 0.0945$) or the postoperative time ($r = 0.555$, $P = 0.1210$) in the recurrent cases, CA 19-9 doubling time was significantly ($r = 0.904$, $P = 0.0008$) correlated with the time from operation until the start of increase in serum CA 19-9 level.

Relationship Between CEA Doubling Time and Survival Time

Significant correlation ($r = 0.414$, $P = 0.0443$) was observed between CEA doubling time and survival time in the inoperable cases. But, in the palliatively operated cases, the CEA doubling time was not correlated with the observation time ($r = 0.502$, $P = 0.0805$) or with length time of the postoperative period ($r = 0.466$, $P = 0.1082$). In the recurrent cases, no correlation was observed between CEA doubling time and survival time ($r = 0.451$, $P = 0.4463$) or length time of the postoperative period ($r = 0.225$, $P = 0.7161$).

There was a significant relationship between CA 19-9 doubling time and CEA doubling time in the group of inoperable cases ($r = 0.748$, $P = 0.0033$), but not in the group of palliatively operated cases ($r = 0.410$, $P = 0.1854$), or recurrent cases ($r = 0.638$, $P = 0.2463$).

TABLE I. Doubling Time of Serum CA 19-9 in Inoperable Cases of Pancreatic Cancer*

Case no.	Age (years) and sex	Tumor location	Liver metastasis	Observation time (days)	Initial serum level[a]		Doubling time	
					CA 19-9 (U/ml)	CEA (ng/ml)	CA 19-9 (days)	CEA (days)
1	93 M	Head	+	8	970	2.0	6.1	3.6
2	78 F	Head	−	32	1,900	3.6	8.3	NSI
3	85 M	Head	−	35	2,785	10.1	58.0	24.8
4	67 M	Head	+	51	18,000	7.3	15.0	8.1
5	79 F	Head	−	58	110	1.2	30.3	NSI
6	80 F	Head	+	63	56,000	12.9	39.7	NSI
7	60 M	Body	+	64	12,000	2.3	32.5	23.6
8	79 F	Tail	+	67	56	32.8	8.7	24.3
9	62 F	Head	+	71	6,400	9.5	46.3	NSI
10	59 F	Head	+	76	190,000	9.9	18.8	22.4
11	84 F	Head	−	77	1,100	13.7	17.9	28.1
12	83 F	Head	−	78	760	2.6	37.0	NSI
13	39 M	Tail	+	85	5	1.0	13.0	NSI
14	78 F	Body	+	85	49	0.9	28.1	NSI
15	57 F	Head	+	88	8,400	1.6	24.7	18.4
16	68 F	Body	+	89	3,800	9.6	10.5	NSI
17	92 F	Body	+	93	310,000	788.6	45.2	151.8
18	68 M	Head	+	106	140	1.0	18.3	38.8
19	75 F	Head	−	107	28	38.0	8.6	51.6
20	84 M	Head	+	108	2,400	15.5	45.5	54.7
21	71 M	Body	−	116	450	5.5	31.6	137.0
22	71 M	Tail	+	116	18,700	3.5	38.1	78.0
23	85 M	Tail	−	116	6,200	14.1	65.6	168.1
24	49 M	Body	+	118	4,800	4.1	40.6	71.0
25	72 F	Head	+	124	11	13.1	NSI	74.4
26	86 F	Head	−	140	1,900	1.0	36.5	NSI
27	76 F	Body	−	155	19	3.3	NSI	NSI
28	61 M	Head	−	156	5	2.0	NSI	NSI
29	82 F	Head	−	184	970	1.2	64.5	70.7
30	61 M	Tail	+	186	6,169	28.0	45.9	18.7
31	74 F	Head	+	192	100,000	49.0	32.2	NSI
32	44 F	Body	+	223	1,400	2.9	22.3	36.7
33	62 M	Body	−	238	89	2.6	191.8	NSI
34	83 F	Head	−	242	1,600	7.4	65.6	141.7
35	73 F	Body	+	278	43	1.1	30.4	53.9
36	46 F	Head	−	278	2,700	4.7	67.1	165.6
37	81 F	Head	−	307	55	1.0	68.1	67.2
38	68 M	Body	+	341	33	1.0	NSI	NSI
39	60 M	Head	−	349	190	4.9	71.2	NSI
40	42 F	Head	+	366	100	1.4	44.7	NSI
41	75 M	Head	+	610	77	1.0	313.0	NSI

*NSI, no significant increase of serum level in relation with time.
[a]Serum level measured at the start of observation.

Relationship of Initial Tumor Marker Level With Survival Time or Doubling Time

Initially measured serum level of CA 19-9 or CEA at the start of observation in the group of inoperable and palliatively operated cases exhibited no relationship with its doubling time or survival time of the patient. There was no correlation between preoperative CA 19-9 or CEA level and time of survival period or postoperative period in the group of recurrent cases with resectable operation.

Correlation of CA 19-9 Doubling Time With Tumor Volume Doubling Time

The tumor volume doubling time could be estimated in 12 cases in this study, and they were 34.8, 44.6, 34.5, 21.2, 47.7, 112.8, 91.9, 70.6, 18.4, 50.6, 231.6, and 39.3 days in each of case numbers 2, 6, 9, 26, 35, 36, 38, 40, 47, 50, 62, and 68 in Tables I and II. This was comparable with the CA 19-9 doubling time in 11 of these cases, except in case number 38. Of these 11 patients, significant correlation ($r = 0.948$, $P < 0.0001$) was ob-

TABLE II. Doubling Time of Serum CA 19-9 in Operated Cases With Pancreatic Cancer*

Case no.	Age (years) and sex	Tumor location	Liver metastasis	Observation time (days)	Post-operative time (days)	Doubling time CA19-9 (days)	Doubling time CEA (days)
Cases with palliative operation, but without resection of the tumor							
42	56 M	Body	+	62	22	20.3	38.8
43	73 M	Body	−	68	58	3.2	12.3
44	69 F	Head	−	80	59	6.3	NSI
45	64 F	Body	+	91	70	40.7	NSI
46	53 M	Head	−	132	73	12.0	14.6
47	71 M	Tail	−	137	96	24.7	152.3
48	48 F	Head	+	182	140	33.6	31.5
49	74 M	Head	−	184	81	NSI	NSI
50	68 F	Head	−	204	174	42.7	92.2
51	53 M	Tail	−	227	187	37.2	NSI
52	67 F	Head	+	237	170	153.5	97.5
53	77 M	Head	−	240	201	NSI	NSI
54	73 M	Body	+	259	188	30.7	27.6
55	59 M	Head	+	297	278	35.5	35.7
56	68 F	Head	−	324	276	NSI	NSI
57	61 M	Head	+	328	305	NSI	125.1
58	72 F	Body	−	355	307	145.2	NSI
59	67 F	Head	−	377	329	79.3	60.8
60	70 M	Body	+	436	381	38.5	105.8
61	69 F	Head	−	525	366	70.0	138.7
62	57 M	Head	−	871	812	137.5	NSI
Cases with recurrence after resectable operation							
63	68 F	Tail	−	263	217	54.9	47.4
64	76 F	Head	+	267	177	14.1	29.8
65	44 M	Head	+	279	239	13.8	54.7
66	40 M	Head	+	494	464	28.6	NSI
67	64 F	Tail	−	586	388	65.5	117.3
68	55 M	Tail	+	624	532	42.3	35.7
69	54 M	Body	−	730	668	34.7	NSI
70	62 F	Head	+	806	766	42.1	NSI
71	64 M	Tail	+	856	849	94.7	NSI
Cases without any recurrence after resectable operation							
72	75 M	Body	−	3498<	3467<	NSI	NSI
73	47 M	Head	−	1721<	1679<	NSI	NSI
74	39 F	Tail	−	4140<	4088<	NSI	NSI
75	50 M	Head	−	3022<	2960<	NSI	NSI

*NSI, no significant increase of serum level in relation with time.

served between tumor volume doubling time and CA 19-9 doubling time

On the other hand, the CEA doubling time was simultaneously obtained in five cases (numbers 35, 36, 47, 50, and 68), and no correlation ($r = 0.399$, $P = 0.5059$) between CEA doubling time and tumor volume doubling time was observed.

Relationship Between Tumor Marker Doubling Time and Sex, Age, or Site of the Lesion of Pancreatic Cancer

No significant difference was observed in the CA 19-9 or CEA doubling time according to the sex, age, or the site of the lesion in patients with pancreatic cancer in this study. Neither the CA 19-9 nor CEA doubling time was significantly different according to the presence or absence of liver metastasis or jaundice; tumor marker doubling time was considered to be a parameter independent of these factors.

DISCUSSION

To promote the eradication of pancreatic cancer, biological characteristics or natural history of this refractory disease must be well elucidated. Through laboratory and clinical studies we have investigated tumor markers for pancreatic cancer. We have evaluated substances produced by pancreatic cancer, developed highly sensitive methods for their measurement [9,10], conducted their immunohistological evaluation [7], and compared their tissue concentrations [8]. We have also assessed the di-

agnostic significance of their immunoassay in serum, pure pancreatic juice [11,12], and cystic fluid of the pancreas [13], and studied DNA ploidy patterns of pancreatic [14], stomach [15], and colon [16] cancer cells.

Although the growth rate of cancer is a very basic and important problem, the method for its precise evaluation has yet to be established. Clinical findings are often simply expressed by obscure terms such as "increased in size or number in comparison with previous findings." Adequate analysis using a more objective scale of the growth rate is needed for accurate understanding of the pathology of cancer.

Collins et al. [17] studied the growth rate of cancer on the assumption that the growth of cancer is exponentially stable and defining the time needed for the tumor volume to increase twofold as the "(tumor volume) doubling time." Following this proposal, Kusuma et al. [18] reported the doubling time of the volume of breast cancer. The tumor volume doubling time was reported to be useful for estimating the malignant potential of gastric smooth muscle tumors [19], and an independent and significant prognostic factor for lung cancer patients [20,21].

Concerning tumor marker doubling time, Staab et al. [22] reported the CEA doubling time in colon cancer. Moreover, Takahashi et al. [23] reported a significant correlation between the CEA doubling time and postoperative survival time among patients with stomach cancer who did not receive chemotherapy. Prostate specific antigen doubling time was reported to be a strong prognostic factor in patients with prostate cancer [24]. Many reports to date have supported an association between the growth rate and the prognosis of various cancers.

In the present study, we examined the tumor marker doubling time in patients with pancreatic cancer. The CA 19-9 or CEA doubling time was significantly correlated with survival time in inoperable cases, and the CA 19-9 doubling time was significantly correlated with postoperative time in cases treated by palliative surgery.

Sheu et al. [25] reported a significant correlation between doubling time of tumor volume and that of serum alpha-fetoprotein level in patients with hepatocellular carcinoma. In some of our patients with pancreatic cancer, the value of tumor marker doubling time was similar to those of the tumor volume doubling time as observed in the patient of the case presentation; the tumor marker doubling time may be an index of the growth rate of pancreatic cancer.

In fact, a number of factors are considered to be clinically involved in the elevation of the serum level of tumor markers, and little may be known about their catabolism or removal from the blood stream. However, the increase in substances produced by pancreatic cancer may reflect the growth of the cancer. Moreover, the faster it grows, the more significantly the tumor marker levels increase.

In other words, the patients of pancreatic cancer cases with short CA 19-9 doubling time, most probably related to rapid growth of the tumor, would be generally associated with short survival time. Or, it could be stated that the pancreatic cancer would be more malignant and prognosis of such malignancy would be poorer, as its tumor marker doubling time is shorter and the growth rate is greater. Our results indicate the clinical usefulness of the CA 19-9 doubling time in prognosis and evaluation of the therapeutic effects in pancreatic cancer.

It was difficult to know the minimum time of observation needed to predict a doubling time accurately through the data in this investigation. And, because presented cases had different intervals or times of measuring tumor markers, analytic comparison of the first two successive measurements between cases or with complete set of measurements could not be established.

The diagnostic usefulness of each tumor marker is related to its sensitivity and specificity in making a diagnosis for cancer. Conversely, the precise method in making a comparative evaluation for tumor marker as a monitoring parameter in the follow-up of patients with cancer has yet to be established. In this study, the CA 19-9 doubling time was calculable in a higher percentage of pancreatic cancer patients and showed a more distinct correlation with survival time than the CEA doubling time, suggesting the greater usefulness of CA 19-9 than that of CEA as a monitoring marker for the follow-up of pancreatic cancer. Therefore, examination of the tumor marker doubling time may be regarded as a method for the evaluation of the usefulness of each tumor marker as a follow-up parameter.

Recently, CA 19-9 and CEA, which have been evaluated mainly as tumor markers, have been shown to function as sugar chain ligands of adhesive molecules [26], and their roles in metastasis of cancer have begun to attract attention on the basis of the speculation that hematogenous metastasis is more likely to occur as their serum levels increase.

Pancreatic cancer cells in culture demonstrate differences in the proliferative ability or producing ability of various substances among clones [27]. Therefore, qualitative and quantitative evaluation of substances produced by pancreatic cancer tissues and, in addition, time-course analysis of biological characteristics in individual cases are considered to provide very important information for the diagnosis or follow-up of all patients with pancreatic cancer.

CONCLUSIONS

Doubling time of serum CA 19-9 in patients with pancreatic cancer is considered to be associated with their survival time, and may probably prove to be valuable as

a significant prognostic indicator, in evaluating the effects of operative treatment, as early suggestion or detection of a postoperative recurrence, or in the assessment of the prognosis of patients with pancreatic cancer. Moreover, analysis of the growth process according to the tumor marker doubling time as the cancer advance could be a useful approach in clarification of the pathological character of this hard-to-treat disease.

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